Pharmacokinetic-pharmacodynamic based economic models of rituximab for follicular lymphoma

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Health Economics

- The branch of economics associated with issues relating to scarcity in the allocation of resources for health care.
- Cost-utility analyses estimate the ratios between costs and benefits of health-related interventions.
- Benefits are usually expressed in terms of QALYs (Quality-adjusted life years).

Health Economic Evaluation

- Usually reliant on modelling to give an outcome expressed as incremental £/QALY gained.
  - Data from clinical trial(s).
  - Estimates for effectiveness, costs and health utilities.
- Increasing need for early estimations of economic value at a time when confirmatory trial evidence does not exist.
  - Value-based pricing.
  - Internal decisions informing drug development.

PKPDPE Modelling

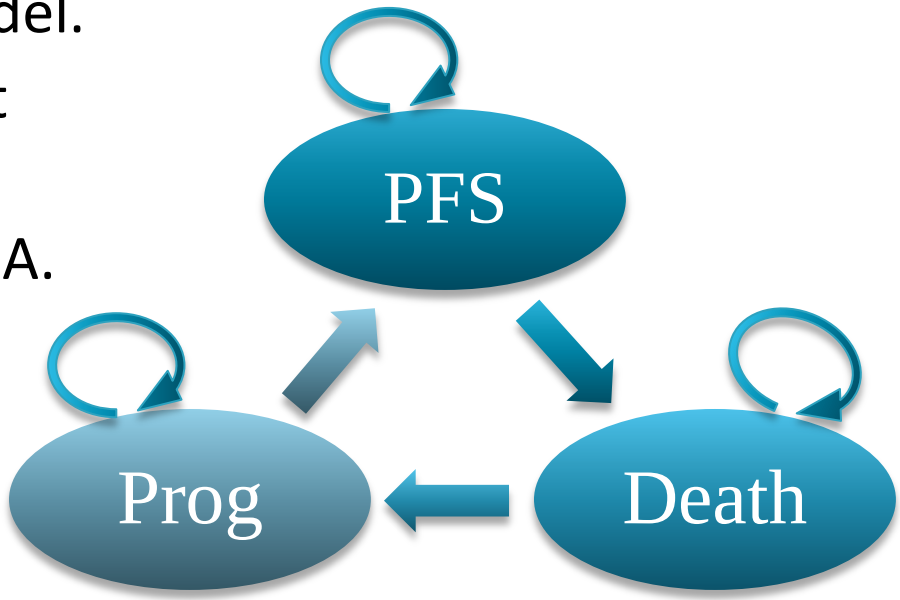
- Link together established population PKPD models with health economic models by simulating the outcome of clinical trials.
- £/QALY can thus be reached as an outcome measure.
- Trial design can be made, based on the actual end criteria by which success will ultimately be judged.
- Amenable to Value of Information analysis.
  - Informing trial design.
  - Identification of subgroups etc.

Case Study - Rituximab

- Rituximab is a monoclonal antibody used in the treatment of follicular lymphoma.
- Separate evidence available for its PK, PD (progression-free survival) and cost-effectiveness.
- Aim is to make use of these data to develop a PKPDPE model.
  - Proof of concept exercise.
  - Compare PKPDPE output with industry submission to NICE.

Rituximab Model - overview

- PK model – Ng et al.
  - Two compartment linear model.
  - BSA and gender as significant covariates.
  - Based on 102 patients with RA.
- PD model – Ternant et al.



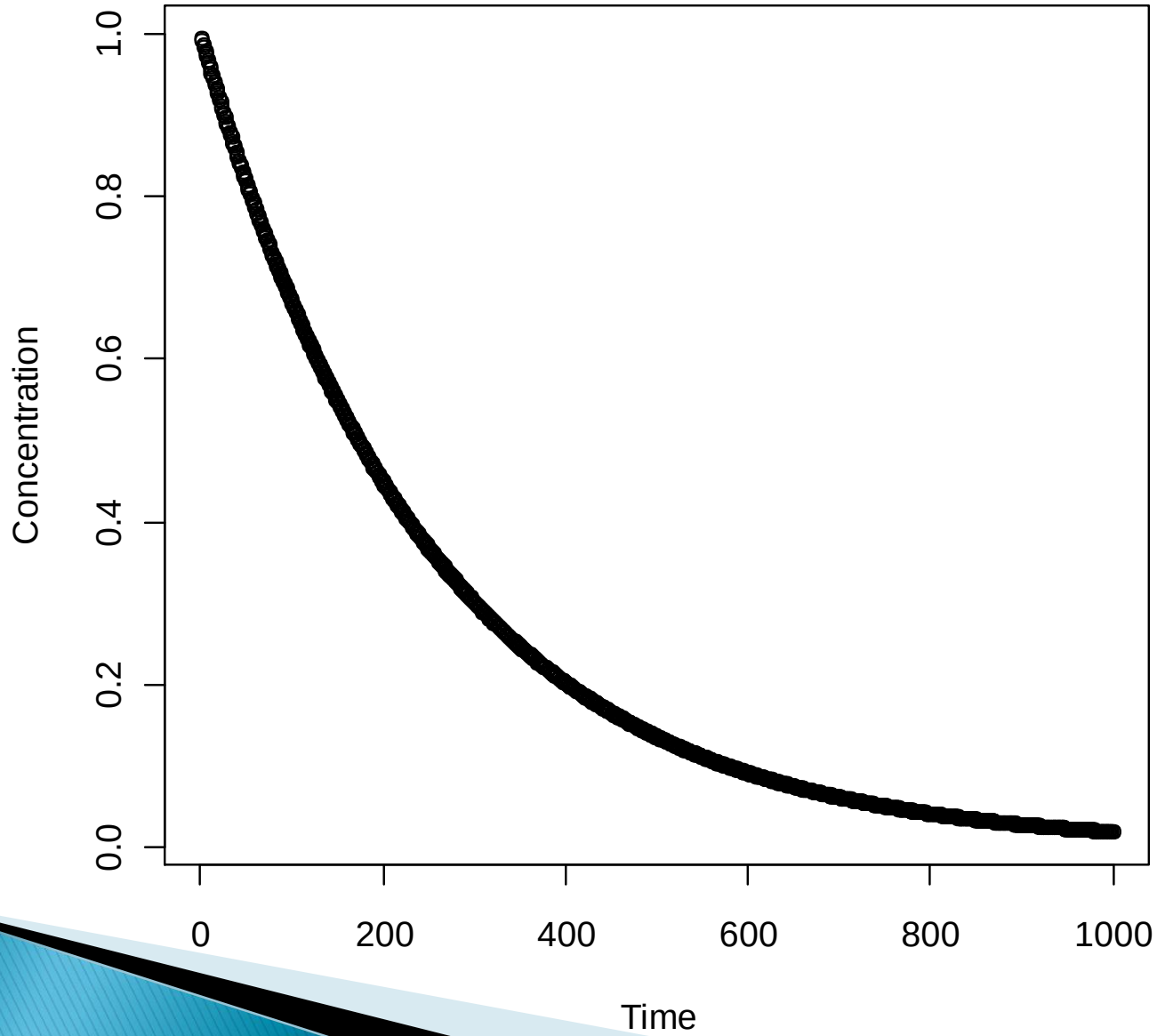
$$Cm(t) = \frac{\int_{t_n}^{t} C(\tau)d\tau}{t - t_n}$$

$$PFS(t) = \exp\left(-\left(\lambda_{max}\left(1 - \frac{Cm^{\gamma}}{Cm_{50}{}^{\gamma} + Cm^{\gamma}}\right)\right)t\right)$$

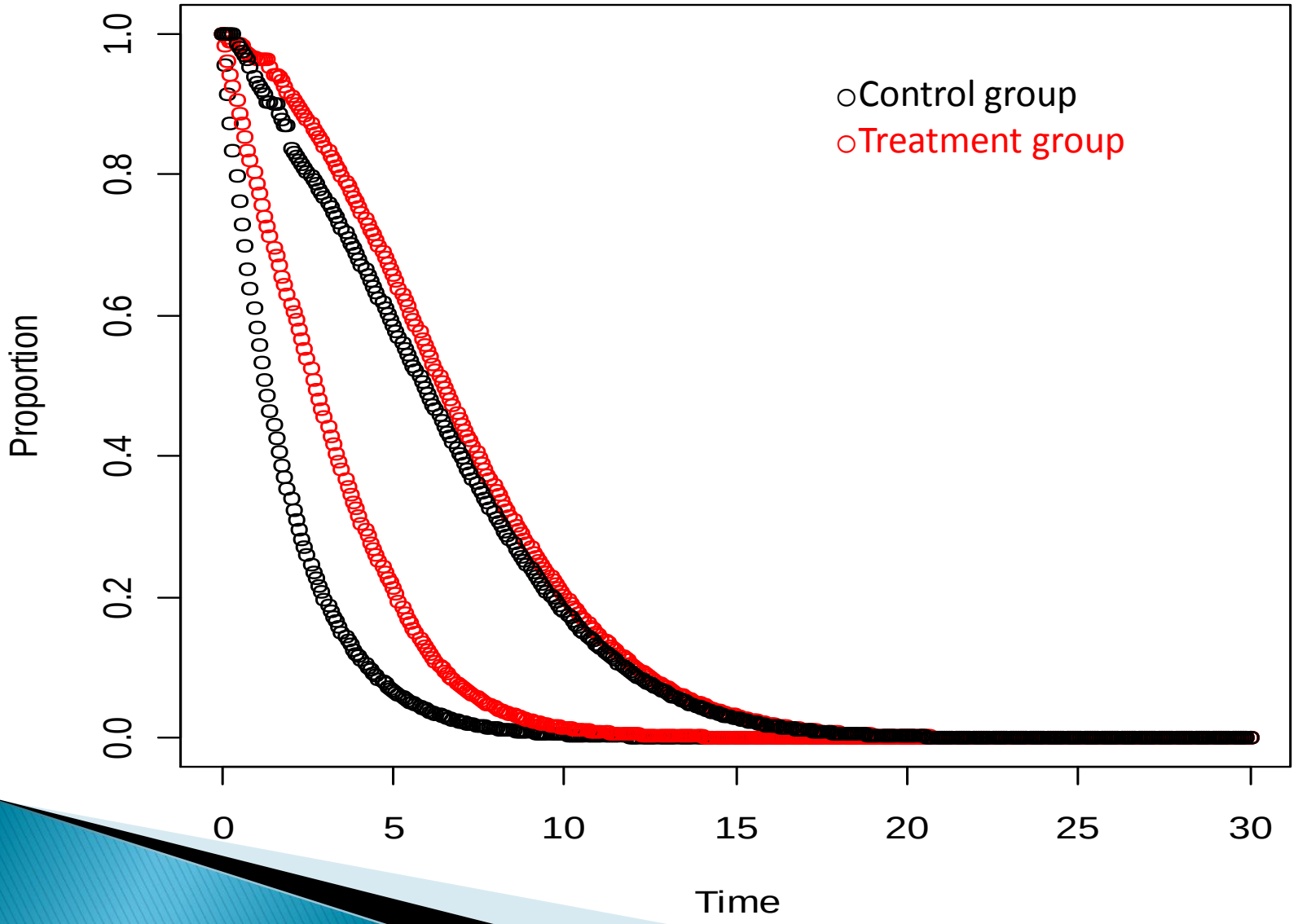
Methods

- Overview:
  - Replicate NICE STA economic model, but substitute trial-reported PFS with PFS derived from PKPD simulation.
- Clinical data:
  - Overall survival data/parameters taken from EORTC 20981 trial.
  - Progression free survival simulated from PKPD model.
- Other parameters are all taken from the NICE STA submission:
  - Trial also provides data on incidences/costs of adverse events.
  - Other costs taken from NHS reference costs.
  - Health utility scores come from an Oxford Outcome Group study.

PK Model – Ng et al



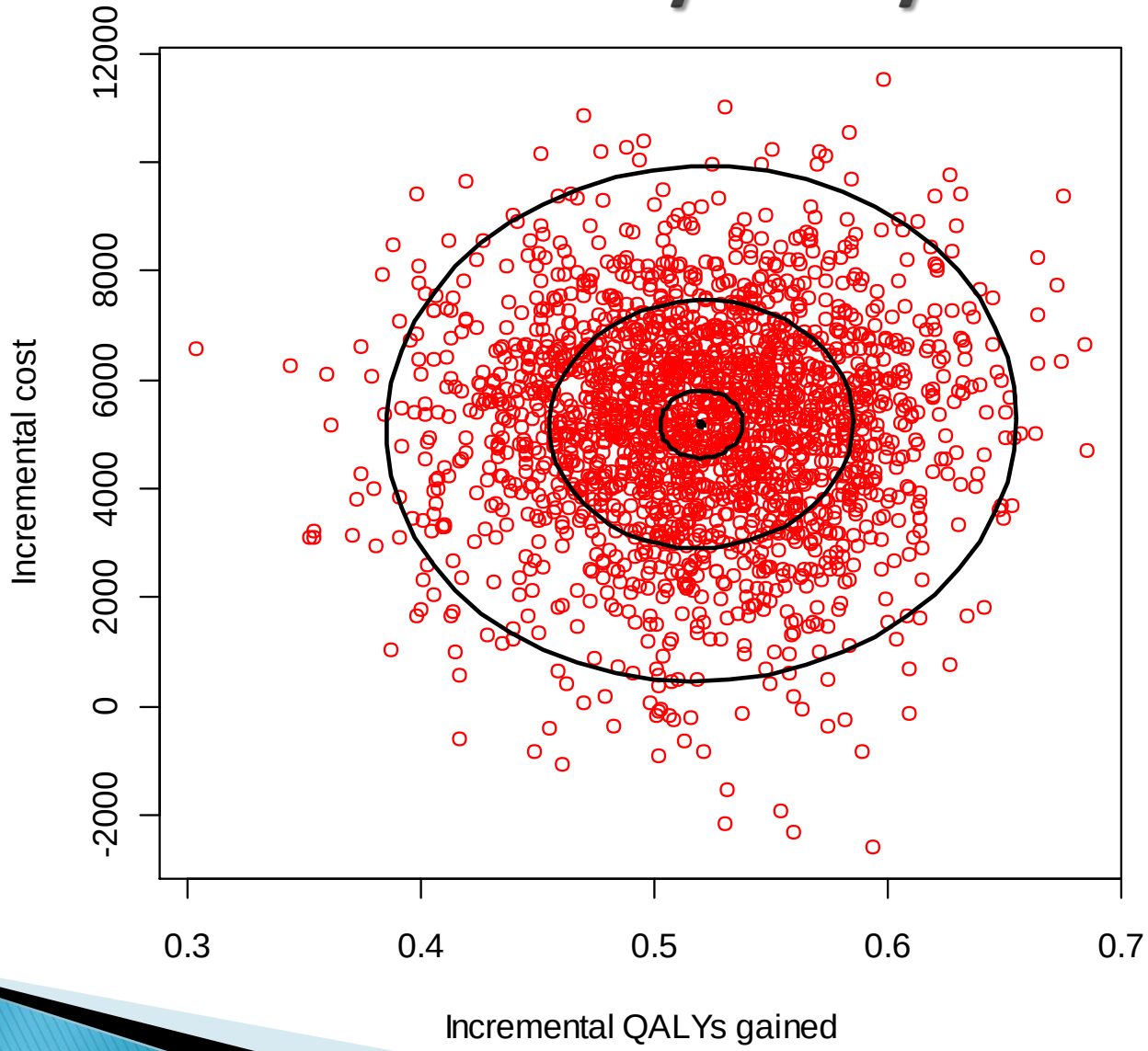
PD Model – Ternant et al



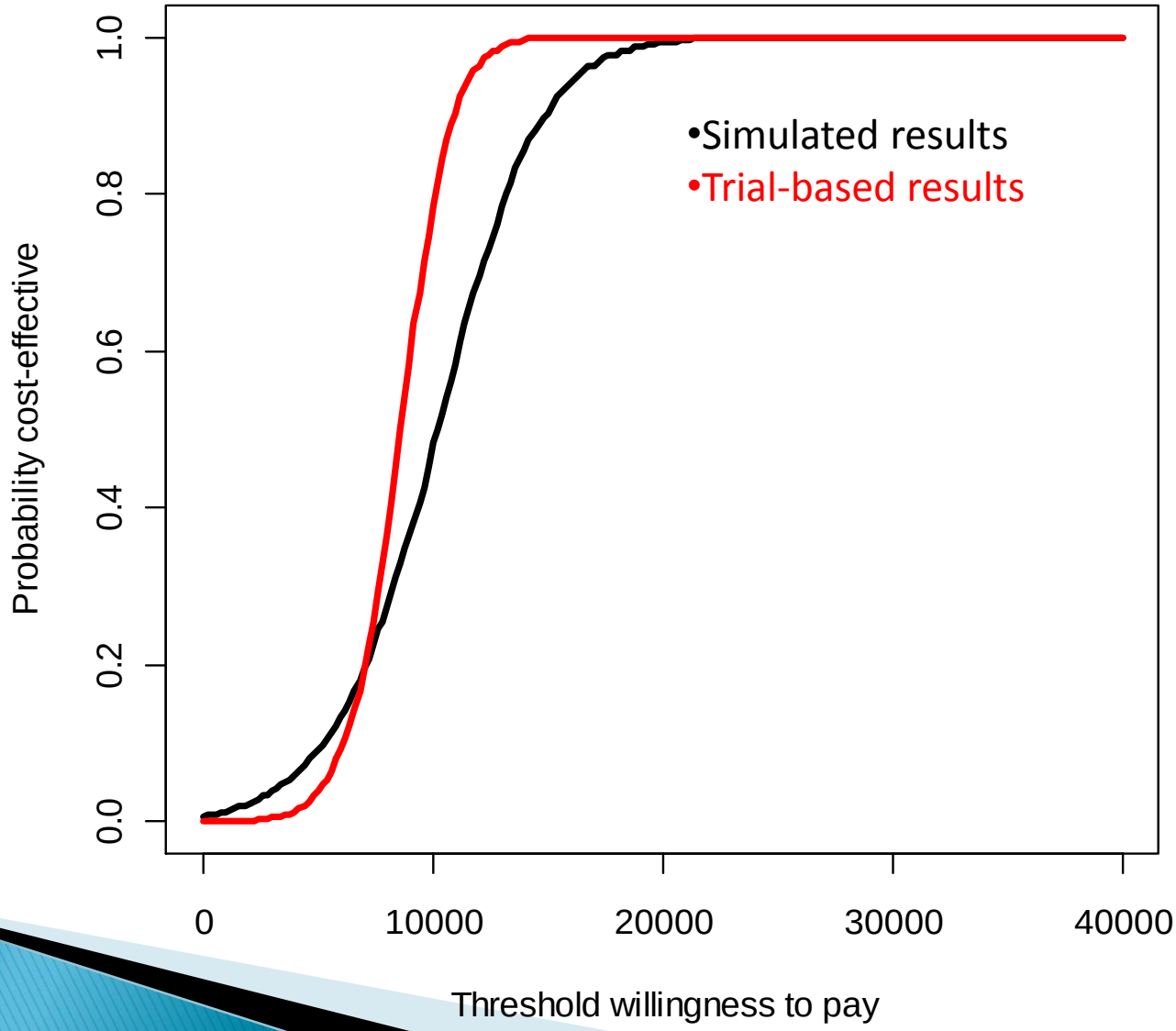
Results

Value	Simulation	Original	95% CR for difference
Median survival – C	5.288	5.214	
Median survival – T	6.267	6.221	
Mean life expectancy – C	5.4026	5.4092	
Mean life expectancy – T	6.5878	6.5998	
Total cost – C	£17,419	£14,722	
Total cost - T	£22,736	£21,608	
Incremental cost	£5,317	£6,886	(-£829,£2,958)
Incremental life years	0.9973	1.0001	
Incremental QALYs	0.5703	0.8919	(0.0027,0.5872)
Incremental cost per QALY	£9,323	£7,721	(-£1,943,£5,955)

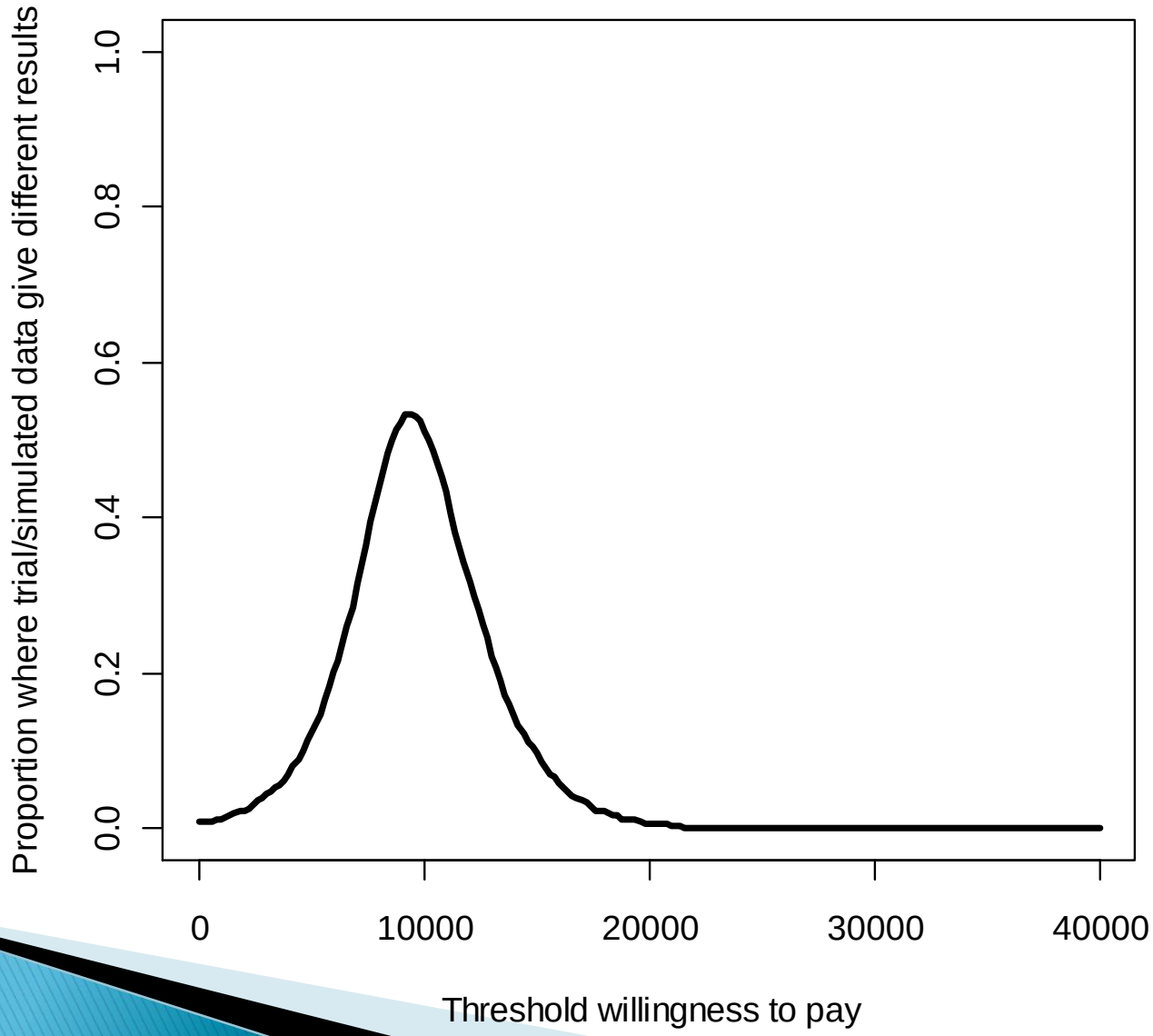
Probabilistic Sensitivity Analysis



Cost-effectiveness Acceptability Curve



Agreement of modelling approaches



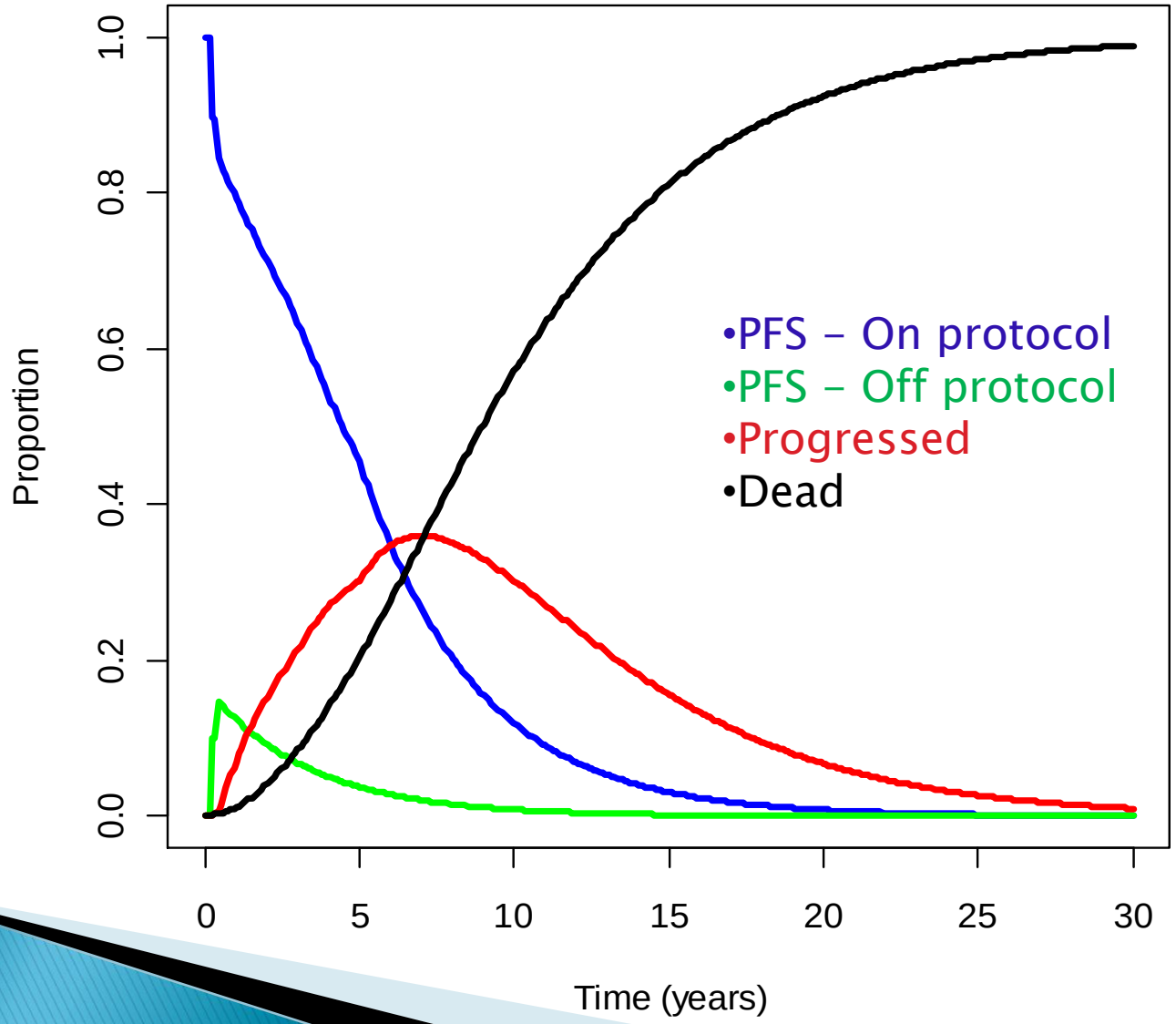
Case study #2: PACIFICO Trial

- Phase III multicentre trial comparing two different Rituximab-Chemotherapy induction regimens (R-CVP and R-FC) for Follicular Lymphoma in Older Patients.
  - Currently recruiting
- Rituximab is used in both the induction and maintenance phases of the treatment.

Methods

- Clinical data:
  - Baseline hazards and response rates for the two chemotherapy regimens taken from a trial comparing FC and CVP.
  - A meta-analysis of trials containing FC or CVP was conducted to obtain information on adverse events and the treatment effect of rituximab.
  - PKPD model provides PFS data, which is combined with all-cause mortality data and data on 2nd line chemotherapy.
- Economic data:
  - Extrapolated to a lifetime horizon of analysis.
  - Taken from previously published economic evaluations.

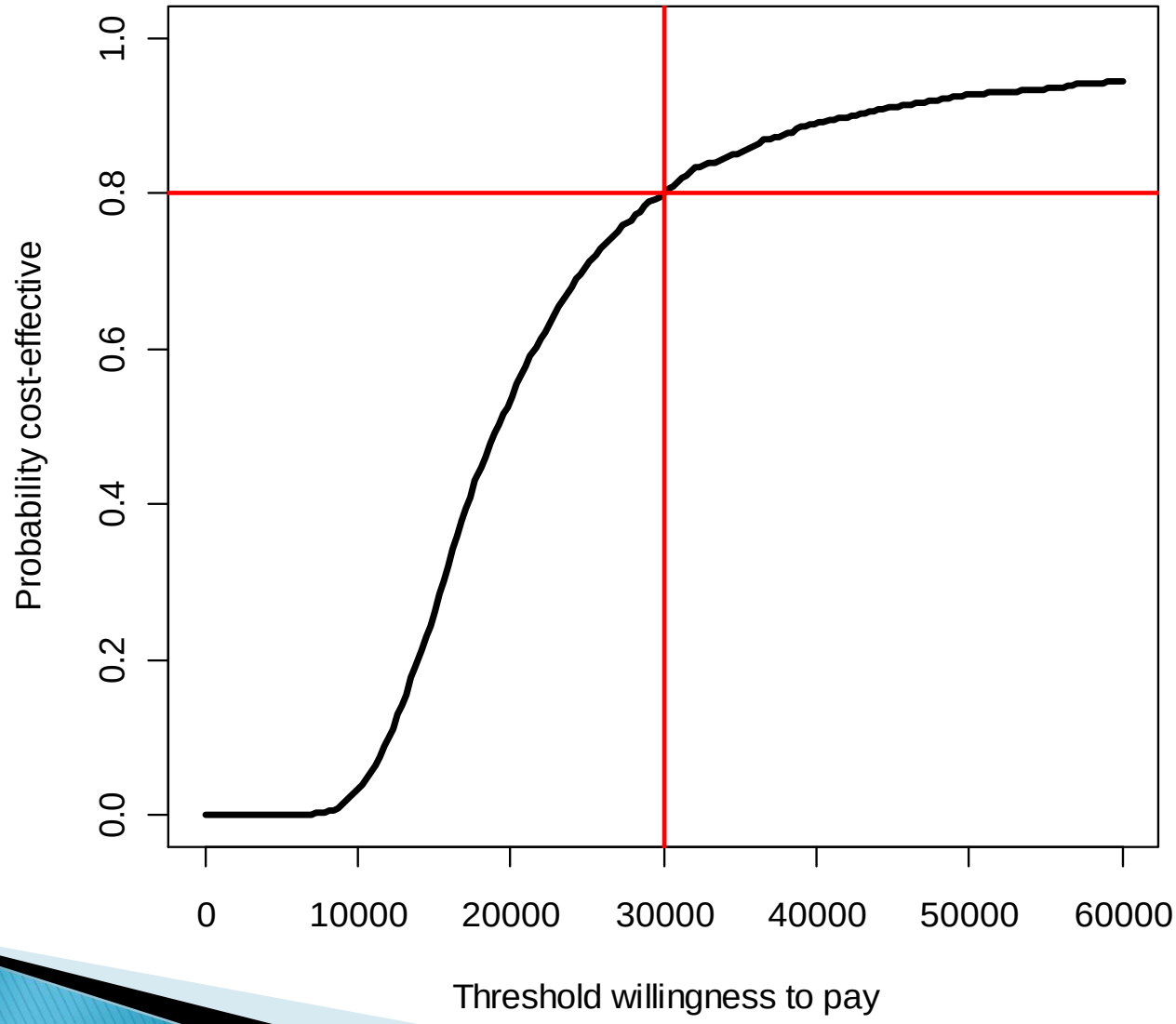
PACIFICO Simulation



Results

Value	R-CVP	R-FC
Median survival	9.008	9.542
Mean life expectancy	10.1577	10.6678
Total cost	£35,833	£41,401
Incremental cost		£5,568
Incremental life years		0.3260
Incremental QALYs		0.2873
Incremental cost per QALY		£19,376

PACIFICO Simulation



Applications

- Clinical trial design - Simulations can help to inform protocol design in many ways:
  - Sample sizes, dosing regimens, important subgroups.
  - Adaptive trial design.
  - Extrapolation of data beyond the time limits of trials.
  - Model protocol deviations (e.g. Non-compliance).
  - Amenable to value of information analysis.

- Inform stop/go decisions.
  - Early estimates of cost-effectiveness.

Other case studies

- Atrial fibrillation - Comparing new anticoagulants with standard therapy (i.e. warfarin).
- Warfarin - Comparing genotype guided dosing algorithms with standard dosing.
- Diabetes - PKPD models with an output of HbA1C levels can be used as an input to economic models.